



**University of
Zurich**^{UZH}

**Zurich Open Repository and
Archive**

University of Zurich
University Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2010

Control of widespread hypertrophic lupus erythematosus with T-cell-directed biologic efalizumab

Navarini, A A ; Kerl, K ; French, L E ; Trüeb, R M

Abstract: HLE features interface dermatitis and epidermal hyperplasia, which are both explainable by T-cell-mediated immunologic effects. Correspondingly, our case responded well to the treatment with efalizumab. While the withdrawal of efalizumab from the market leaves patients with psoriasis many other options for effective therapy, it disproportionately affects patients with T-cell-mediated orphan diseases like refractory HLE.

DOI: <https://doi.org/10.1159/000277614>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-41661>

Journal Article

Published Version

Originally published at:

Navarini, A A; Kerl, K; French, L E; Trüeb, R M (2010). Control of widespread hypertrophic lupus erythematosus with T-cell-directed biologic efalizumab. *Dermatology*, 220(3):249-253.

DOI: <https://doi.org/10.1159/000277614>

Control of Widespread Hypertrophic Lupus Erythematosus with T-Cell-Directed Biologic Efalizumab

Alexander A. Navarini Katrin Kerl Lars E. French Ralph M. Trüeb

Department of Dermatology, University Hospital of Zürich, Zürich, Switzerland

Key Words

Hypertrophic lupus erythematosus · T cells · Efalizumab · CD4

Abstract

Background/Aims: Hypertrophic lupus erythematosus (HLE) produces not only disfiguring and long-lasting skin changes, but also proves to be particularly resistant to therapy. In a patient with a disease refractory to conventional therapy, we observed a predominantly CD4⁺ T cell infiltrate that we sought to target therapeutically. **Methods:** The patient was treated with the CD11a-directed monoclonal antibody efalizumab together with 10 mg isotretinoin and 5 mg prednisone. **Results:** Within 6 months, the inflammatory hyperkeratotic plaques were almost completely healed, with minimal residual erythema and scarring. The cutaneous lupus activity and severity index score decreased from 8 to 4 of a total of 14 points, and pseudoepitheliomatous hyperplasia and CD4 T cell infiltrates within the lesions were reduced. **Conclusion:** HLE features interface dermatitis and epidermal hyperplasia, which are both explainable by T-cell-mediated immunologic effects. Correspondingly, our case responded well to the treatment with efalizumab. While the withdrawal of efalizumab from the market leaves patients with psoriasis many other options for effective therapy,

it disproportionately affects patients with T-cell-mediated orphan diseases like refractory HLE. Copyright © 2010 S. Karger AG, Basel

Case Report

A 43-year-old male painter consulted us for long-standing, disfiguring and painful plaques on his sun-exposed lower arms and face. The development of the lesions had begun 18 years prior to presentation. Intensely inflamed and hyperkeratotic plaques were observed on both extensor sides of the lower arms, sparing the wristwatch area, on the ridge of the nose, and on both helices and cheeks (fig. 1a). A biopsy revealed hyperkeratotic, pseudoepitheliomatous hyperplasia of the epidermis with interface and deep lymphocytic infiltration, and PAS⁺ thickening of the basal membrane (fig. 1c). Antinuclear, anti-DNA and SS-A and SS-B antibodies were in the normal range. On the basis of the clinical presentation and histology, the diagnosis of chronic cutaneous HLE was made. The patient did not fulfill the American College of Rheumatology criteria for systemic lupus erythematosus (SLE). Previously, therapeutic trials with high-potency topical corticosteroids in combination with keratolytic agents, cryotherapy, oral prednisone, hydroxychloroquine,

dapsone, azathioprine and cyclosporine had been ineffective. Partial disease control was achieved only by a combination of systemic prednisone with azathioprine and isotretinoin. Azathioprine was subsequently substituted by mycophenolate mofetil. After 4 years, however, the efficacy was lost and the plaques recurred.

Since cutaneous lupus erythematosus is mainly T cell mediated [1, 2] and we had identified substantial CD4⁺ lymphocytic infiltrates in our patient's lesions (fig. 1c), we chose at this point to treat the patient with the T-cell-blocking agent efalizumab, which was available at the time for the treatment of plaque-type psoriasis. Efalizumab is a recombinant humanized IgG1 monoclonal antibody that specifically targets T cells, leading to the subsequent inhibition of T cell activation. The efalizumab treatment (initial dose of 0.8 mg/kg body weight followed by 1 mg/kg body weight weekly) was initiated in February 2008, and mycophenolate mofetil was stopped after 2 months of overlap with efalizumab, while the treatment with 5 mg prednisone and 10 mg isotretinoin was continued. Within 6 months, the inflammatory hyperkeratotic plaques were almost completely healed, with minimal residual erythema and scarring (fig. 1a, b). A biopsy during the efalizumab treatment showed a significant reduction in pseudoepitheliomatous hyperplasia and CD4⁺

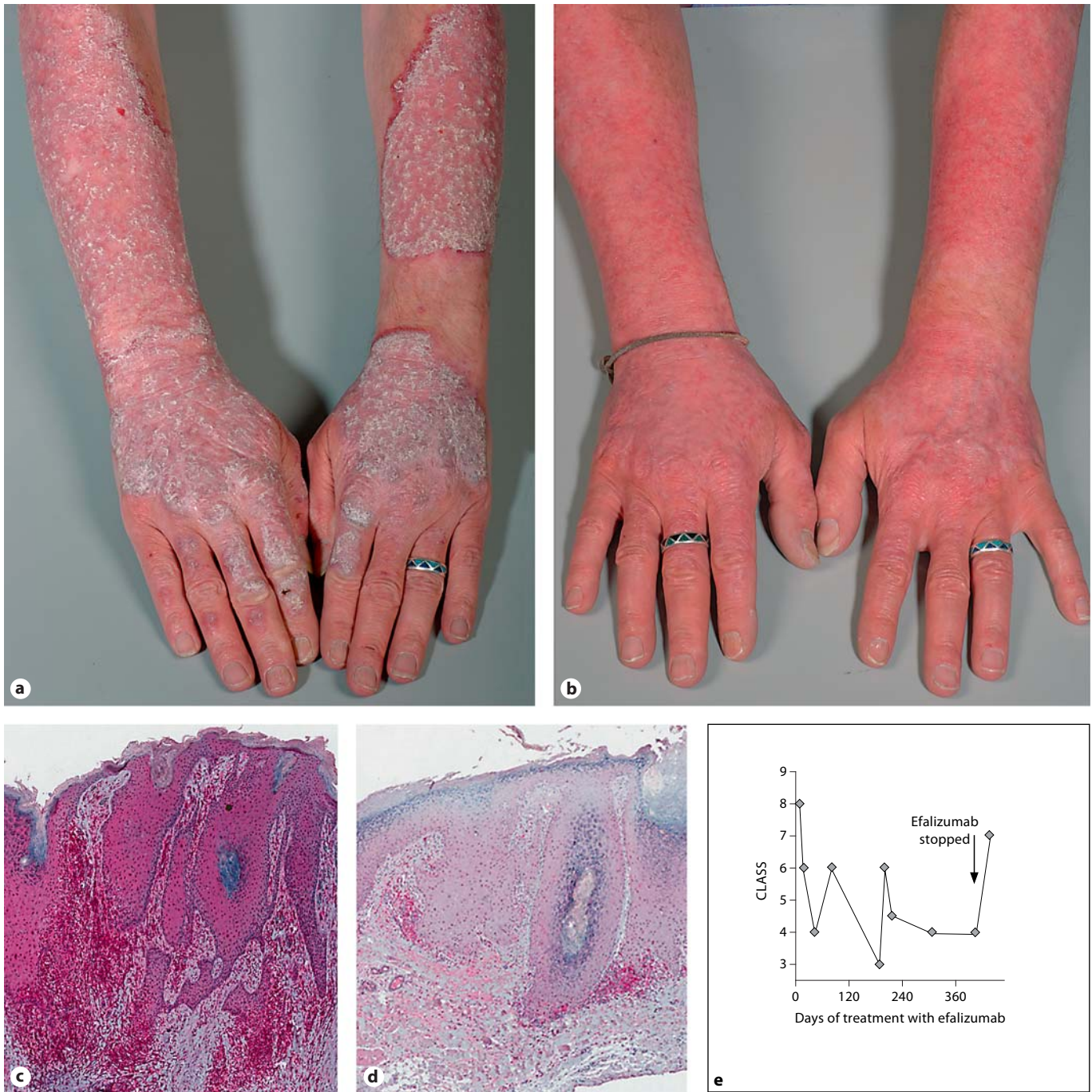


Fig. 1. Lower arms of the patient in November 2007 (a) and after 6 months of efalizumab in August 2008 (b). CD4 (red cells) and hematoxylin-eosin stain of a plaque before treatment (c) and after 10 months of efalizumab (d). e CLASS during treatment with efalizumab. Arrow: stop of efalizumab treatment.

T cell infiltrates (fig. 1d). The clinical disease activity, as assessed by the cutaneous lupus activity and severity score (CLASS) [3], decreased from 8 to 4 (fig. 1e), reflecting persisting scars and low-grade erythema. However, reported cases (3 confirmed, and 1 unconfirmed but suspected case) of the demyelinating disease progressive multifocal leukoencephalopathy [4] have resulted in efalizumab withdrawal from sales in Switzerland in the spring of 2009, and the treatment of our patient was suspended, resulting in a flare of disease activity within 2 weeks (fig. 1e). We did not observe any side effects such as arthralgia or new autoantibodies during or after the therapy with efalizumab.

Concept of HLE: Epidermal Hyperplasia and Interface Dermatitis

HLE or verrucous lupus erythematosus was first described in 1942 by Bechet [5] as a very rare form of cutaneous lupus, usually as a manifestation of discoid, but in rare cases also of subacute cutaneous or SLE. It manifests itself in sharply demarcated, livid-to-intensely-erythematous papules or broadly based plaques with keratotic surfaces, with residual atrophic scars upon regression. The extensor side of the forearms, the face and the upper back can be involved. In the literature, the description varies somewhat from squamous, violet and painful papules and blackish hyperkeratotic ulcers [6] to depigmented atrophic plaques on the back, hyperkeratotic nodular papules on the upper extremities [7] and disseminated keratoacanthoma-like papulonodular verrucous lesions [8]. In histology, follicular hyperkeratosis with hydropic changes within the basal membrane and periadnexal lymphocytic infiltrates are found. Almost always, epidermal hyperplasia and vacuolar degeneration of the basal membrane are found. In direct immunofluorescence, most patients show IgG and IgM on the dermoepidermal border [8, 9]. The closest differential diagnoses are spinocellular carcinoma and verrucous lichen planus. Both diagnoses can be concomitant with HLE [7, 10, 11], and spinocellular carcinoma in particular has been described to develop within verrucous HLE plaques after sun exposure. In addition, keratoacanthoma, hypertrophic actinic keratosis, nodular prurigo and psoriasis vulgaris must be ruled out [6, 8].

HLE has the feature of epidermal hyperplasia in common with psoriasis. Recently, interleukin-21 [12] and interleukin-22 [13] have been shown to be responsible for this phenomenon in psoriasis by activating the proliferation of keratinocytes via sustained extracellular signal-regulated kinases 1 and 2, which are both overexpressed in psoriatic skin. Besides inducing epidermal proliferation, the CD4+ T-helper-cell-produced interleukin-21 controls the differentiation and functional activity of T cells, B cells and NK cells, and renders effector T cells resistant to T regulatory immunosuppression [14]. It also stimulates epithelial cells and fibroblasts to produce inflammatory mediators. Interestingly, interleukin-21 has been found to be overexpressed in lupus erythematosus [15] and positively implicated in the pathogenesis in a murine lupus model [16], and even an interleukin-21 receptor polymorphism has been identified as an independent risk factor for lupus erythematosus [17]. Interleukin-21 could be partly responsible as well for the readily observable, long-lasting immune infiltrates in HLE, as overexpression of this cytokine has resulted in the massive accumulation of CD8+ memory T cells [18]. Interleukin-22, on the other hand, does not seem to play an important role in lupus, as its serum levels have even been found to be lowered [19]. Therefore, considering the still very limited data available on lupus erythematosus and epidermal hyperplasia, treatment with monoclonal antibodies against interleukin-21 could be a valuable option for HLE by addressing both the T cell infiltrate and epidermal hyperplasia.

A pathognomonic histological feature of cutaneous lupus erythematosus is the involvement of the dermoepidermal junction zone. Lymphocytes line up and can obscure this region in a 'lichenoid' histological pattern [20]. Damage to this area leads to later scarring caused by the disease, very much unlike psoriasis where involved skin is typically able to heal without leaving a trace, even after severe momentary pathology. In all types of lupus, inflammation shows phototropism, which has recently been identified to correlate with intercellular adhesion molecule 1 expression due to UVA and UVB rays [21], attracting lymphocytes in the upper dermis. The infiltrate in cutaneous lupus erythematosus has been shown to consist mostly of T cells with a predominance of CD4+ over CD8+ T cells [1, 2]. When the

lichenoid pattern and damage to the dermoepidermal junction zone becomes prolonged, atrophic scarring occurs, possibly by the detrimental action of granzyme B expressing skin-homing CLA+CD8+ T cells [22]. A mixed dermal infiltrate of dendritic cells (DC) and lymphocytes is associated with this process, in a patchy or perivascular pattern. Especially the plasmacytoid DC (pDC), whose principal role is to secrete type I interferon, are present in cutaneous lupus erythematosus lesions, underlining the essential role of type I interferon in lupus erythematosus, which has been elegantly and convincingly shown [23–25]. Although the exact role of pDC in lupus is unclear, it is known that they are activated by DNA complexed with antimicrobial peptides [26], a process that could possibly be enhanced by anti-DNA antibodies [27, 28]. The accumulation of pDC and the expression of the myxovirus protein A is associated in cutaneous lesions of lupus, indicating a local production of type I interferons [29]. Because type I interferon has pleiotropic effects on the immune system, it can greatly enhance the accumulation of lymphocytes such as autoreactive T cells in the dermoepidermal junction of the skin by induction of chemokine (C-X-C motif) ligand (CXCL) 9, IP-10/CXCL10 and CXCL11, all of which recruit CXC-receptor-3-expressing lymphocytes such as Th1 CD3+CD4+ and CD3+CD8+ T cells. With the major histocompatibility complex class II activation pattern of CD3+CD4+ T cells that is found in both diseases, a pathogenetic relationship has been shown between cutaneous and SLE [30], and systemic and discoid lupus erythematosus are considered two ends of a spectrum.

Modern Therapeutic Options for Cutaneous Lupus Erythematosus

First-line agents in the management of cutaneous lupus erythematosus are UVR protection, high-potency topical corticosteroids and antimalarials. Systemic retinoids are second in line, and immunomodulatory/immunosuppressive drugs including systemic steroids are considered third-line agents [31–33]. Of all the forms of lupus erythematosus, the hypertrophic form has proven to be particularly resistant to therapy. To control HLE, an effective treatment must address both the specific inflammatory infiltrate as well as the

enormous thickening of the epidermis, which both seem to be elicited by inflammatory T cells. With the advent of new biologic agents for the treatment of medical conditions for which no other satisfactory treatment is available, new avenues have opened up as well for a pathogenetically oriented treatment of orphan diseases. To determine the extent of accuracy with which a theory describes the pathogenesis, an adapted medical treatment addressing the suspected disease mediators can yield the answers. As early as 1996, in a groundbreaking case series, 5 cases of severe cutaneous lupus erythematosus had been successfully treated with the chimeric CD4 monoclonal antibody cM-T412 [34]. As an early treatment event, the authors reported a nearly complete loss of cutaneous inflammatory activity after each infusion cycle. Interestingly, autoantibody titers did not decrease except in 1 patient.

More subtle treatment trials for lupus erythematosus were later performed with the agent efalizumab. This molecule is an immunomodulating, specific, recombinant humanized IgG1 antibody for CD11a, the α -subunit of lymphocyte function antigen 1 (LFA-1). By blocking the binding of LFA-1 to intercellular adhesion molecule 1, efalizumab inhibits the adhesion of leukocytes to other cell types and interferes with the migration of T lymphocytes to the sites of inflammation (including psoriatic skin plaques). Efalizumab has no direct depleting effect, and lymphopenia is not a regular side effect. As an additional proof of concept without the rather drastic effects of abolishing the whole CD4+ T cell subset [34] and its beneficial protective responses, a successful therapy of discoid lupus erythematosus with efalizumab was shown in one open study and in case reports [3, 35, 36]. Along with its efficacious action on T cells, this drug can also alter DC populations in skin [37].

Another lymphocyte function antigen protein is currently put to medical use in the form of an immunomodulatory receptor Fc fusion protein called alefacept. This

molecule consists of the first extracellular domain of LFA-3 fused to the human IgG1 hinge, CH2 and CH3 domains. It has been shown to bind preferentially to lesional T cells mainly via the costimulatory and adhesive surface protein CD2, which is usually expressed on T and NK cells. Because of their immunoglobulin fusion part, Fc-receptor-positive (CD16) cells bind to targeted lesional T cells and increase extracellular signal-regulated kinase phosphorylation, upregulate the cell surface expression of the activation marker CD25 and induce the release of granzyme B. This eventually leads to an apoptosis of CD2+ target T cells [38], which can lead to relevant but reversible lymphopenia during treatment [39]. However, to our knowledge, no trials have been performed with alefacept for lupus erythematosus, except for the observation that during the treatment of psoriasis with alefacept, a coexistent subacute cutaneous lupus erythematosus did not exacerbate [38].

A monoclonal humanized antibody against the α_4 -subunit of the β_1 -integrin is called natalizumab. It represents the first drug in the class of selective adhesion inhibitors and blocks the adhesion of lymphocytes to vascular cell adhesion molecule 1 or mucosal vascular addressin cell adhesion molecule 1 [40]. In addition, it can modulate inflammatory reactions by inhibiting the binding of α_4 -positive leukocytes with fibronectin and osteopontin. It has been shown to decrease the CD4+/CD8+ ratio in the peripheral blood and cerebrospinal fluid. This antibody might be another candidate for treating lupus erythematosus; however, it too is haunted by the danger of progressive multifocal leukoencephalopathy like its counterpart efalizumab.

Not all types of lupus must be addressed by T-cell-directed therapy. Elevated autoantibodies against the nucleus, double-stranded DNA or ribonuclear particles (SS-A/B) are an important cornerstone in the diagnosis of SLE and subacute cutaneous lupus erythematosus. Therefore, the

pathogenesis of both SLE and subacute cutaneous lupus, but probably not of cutaneous lupus and HLE, involves a role for pathogenic B cells. Because depleting or blocking B cells therefore seems to be a promising therapeutic strategy, many clinical trials are currently ongoing. In a recent review [41], in total 17 completed clinical trials enrolling 973 patients and 5 ongoing studies with an anticipated enrollment of 785 patients were analyzed. B-cell-depleting therapies with the monoclonal antibodies rituximab and epratuzumab resulted in good therapeutic effects, unlike treatment with the B cell tolerogen LJP 394, which did not demonstrate much clinical benefit. Studies targeting costimulatory pathways have shown variable results; clinical trials with anti-CD40L antibody were terminated because of thromboembolic events, whereas studies targeting the B7-CD28 pathway seem promising. Anticytokine agents against B lymphocyte stimulator, interleukin-10 and -6, and interferon- α are all interesting agents whose effects on SLE are not certain yet [41].

Taken together, our patient's HLE had been controlled by the T-cell-directed efalizumab until the agent was taken from the market. The options for directed and pathogenetically adapted therapy are widening for lupus and its rarer forms. Biologic therapy is not limited to targeting single cell types or cytokines, but can break the whole pathogenetic chain, which in this case involved lymphocytic infiltrates and resulting T-cell-dependent epidermal hyperplasia. While the withdrawal of efalizumab from the market leaves patients with psoriasis many other options for effective therapy, it disproportionately affects patients with T-cell-mediated orphan diseases like refractory HLE.

Acknowledgment

This study was supported by the Department of Dermatology, University Hospital of Zürich, Switzerland.

References

- 1 Kohchiyama A, Oka D, Ueki H: T cell subsets in lesions of systemic and discoid lupus erythematosus. *J Cutan Pathol* 1985;12:493–499.
- 2 Synkowski DR, Provost TT: Characterization of the inflammatory infiltrate in lupus erythematosus lesions using monoclonal antibodies. *J Rheumatol* 1983;10:920–924.
- 3 Usmani N, Goodfield M: Efalizumab in the treatment of discoid lupus erythematosus. *Arch Dermatol* 2007;143:873–877.
- 4 Pugashetti R, Koo J: Efalizumab discontinuation: a practical strategy. *J Dermatolog Treat* 2009;20:132–136.

- 5 Bechet PE: Lupus erythematosus hypertrophicus et profundus. *Arch Dermatol Syph* 1942;45:33–39.
- 6 Otani A: Lupus erythematosus hypertrophicus et profundus. *Br J Dermatol* 1977;96:75–78.
- 7 Vinciullo C: Hypertrophic lupus erythematosus: differentiation from squamous cell carcinoma. *Australas J Dermatol* 1986;27:76–82.
- 8 Uitto J, Santa Cruz DJ, Eisen AZ, Leone P: Verrucous lesion in patients with discoid lupus erythematosus: clinical, histopathological and immunofluorescence studies. *Br J Dermatol* 1978;98:507–520.
- 9 Santa Cruz DJ, Uitto J, Eisen AZ, Prioleau PG: Verrucous lupus erythematosus: ultrastructural studies on a distinct variant of chronic discoid lupus erythematosus. *J Am Acad Dermatol* 1983;9:82–90.
- 10 Romero RW, Nesbitt LT Jr, Reed RJ: Unusual variant of lupus erythematosus or lichen planus: clinical, histopathologic, and immunofluorescent studies. *Arch Dermatol* 1977;113:741–748.
- 11 Perniciaro C, Randle HW, Perry HO: Hypertrophic discoid lupus erythematosus resembling squamous cell carcinoma. *Dermatol Surg* 1995;21:255–257.
- 12 Caruso R, Botti E, Sarra M, Esposito M, Stolfi C, Diluvio L, Giustizieri ML, Pacciani V, Mazzotta A, Campione E, Macdonald TT, Chimenti S, Pallone F, Costanzo A, Monteleone G: Involvement of interleukin-21 in the epidermal hyperplasia of psoriasis. *Nat Med* 2009;15:1013–1015.
- 13 Zheng Y, Danilenko DM, Valdez P, Kasman I, Eastham-Anderson J, Wu J, Ouyang W: Interleukin-22, a T_H17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. *Nature* 2007;445:648–651.
- 14 Monteleone G, Pallone F, Macdonald TT: Interleukin-21 as a new therapeutic target for immune-mediated diseases. *Trends Pharmacol Sci* 2009;30:441–447.
- 15 Ettinger R, Kuchen S, Lipsky PE: The role of IL-21 in regulating B cell function in health and disease. *Immunol Rev* 2008;223:60–86.
- 16 Herber D, Brown TP, Liang S, Young DA, Collins M, Dunussi-Joannopoulos K: IL-21 has a pathogenic role in a lupus-prone mouse model and its blockade with IL-21R.Fc reduces disease progression. *J Immunol* 2007;178:3822–3830.
- 17 Webb R, Merrill JT, Kelly JA, Sestak A, Kaufman KM, Langefeld CD, Ziegler J, Kimberly RP, Edberg JC, Ramsey-Goldman R, Petri M, Reveille JD, Alarcon GS, Vila LM, Alarcon-Riquelme ME, James JA, Gilkeson GS, Jacob CO, Moser KL, Gaffney PM, Vyse TJ, Nath SK, Lipsky P, Harley JB, Sawalha AH: A polymorphism within IL21R confers risk for systemic lupus erythematosus. *Arthritis Rheum* 2009;60:2402–2407.
- 18 Allard EL, Hardy MP, Leignadier J, Marquis M, Rooney J, Lehoux D, Labrecque N: Overexpression of IL-21 promotes massive CD8+ memory T cell accumulation. *Eur J Immunol* 2007;37:3069–3077.
- 19 Cheng F, Guo Z, Xu H, Yan D, Li Q: Decreased plasma IL-22 levels, but not increased IL-17 and IL-23 levels, correlate with disease activity in patients with systemic lupus erythematosus. *Ann Rheum Dis* 2009;68:604–606.
- 20 Johnson-Huang LM, McNutt NS, Krueger JG, Lowes MA: Cytokine-producing dendritic cells in the pathogenesis of inflammatory skin diseases. *J Clin Immunol* 2009;29:247–256.
- 21 Stephansson E, Ros AM: Expression of intercellular adhesion molecule-1 (ICAM-1) and OKM5 in UVA- and UVB-induced lesions in patients with lupus erythematosus and polymorphous light eruption. *Arch Dermatol Res* 1993;285:328–333.
- 22 Wenzel J, Uerlich M, Wörrenkämper E, Freutel S, Bieber T, Tüting T: Scarring skin lesions of discoid lupus erythematosus are characterized by high numbers of skin-homing cytotoxic lymphocytes associated with strong expression of the type I interferon-induced protein Mx α . *Br J Dermatol* 2005;153:1011–1015.
- 23 Blanco P, Palucka AK, Gill M, Pascual V, Banchereau J: Induction of dendritic cell differentiation by IFN- α in systemic lupus erythematosus. *Science* 2001;294:1540–1543.
- 24 Kim T, Kanayama Y, Negoro N, Okamura M, Takeda T, Inoue T: Serum levels of interferons in patients with systemic lupus erythematosus. *Clin Exp Immunol* 1987;70:562–569.
- 25 von Wussow P, Jakschies D, Hartung K, Deicher H: Presence of interferon and anti-interferon in patients with systemic lupus erythematosus. *Rheumatol Int* 1988;8:225–230.
- 26 Lande R, Gregorio J, Facchinetti V, Chatterjee B, Wang YH, Homey B, Cao W, Su B, Nestle FO, Zall T, Mellman I, Schröder JM, Liu YJ, Gilliet M: Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide. *Nature* 2007;449:564–569.
- 27 Båve U, Magnusson M, Eloranta ML, Perers A, Alm GV, Rönnblom L: Fc gamma RIIa is expressed on natural IFN- α -producing cells (plasmacytoid dendritic cells) and is required for the IFN- α production induced by apoptotic cells combined with lupus IgG. *J Immunol* 2003;171:3296–3302.
- 28 Vallin H, Perers A, Alm GV, Rönnblom L: Anti-double-stranded-DNA antibodies and immunostimulatory plasmid DNA in combination mimic the endogenous IFN- α inducer in systemic lupus erythematosus. *J Immunol* 1999;163:6306–6313.
- 29 Wenzel J, Wörrenkämper E, Freutel S, Henze S, Haller O, Bieber T, Tüting T: Enhanced type I interferon signaling promotes Th1-biased inflammation in cutaneous lupus erythematosus. *J Pathol* 2005;205:435–442.
- 30 Wouters CH, Diegenant C, Ceuppens JL, Degreef H, Stevens EA: The circulating lymphocyte profiles in patients with discoid lupus erythematosus and systemic lupus erythematosus suggest a pathogenetic relationship. *Br J Dermatol* 2004;150:693–700.
- 31 Ruzicka T, Meurer M, Bieber T: Efficiency of acitretin in the treatment of cutaneous lupus erythematosus. *Arch Dermatol* 1988;124:897–902.
- 32 Callen JP: Management of antimalarial-refractory cutaneous lupus erythematosus. *Lupus* 1997;6:203–208.
- 33 Dooley MA, Ginzler EM: Newer therapeutic approaches for systemic lupus erythematosus: immunosuppressive agents. *Rheum Dis Clin North Am* 2006;32:91–102, ix.
- 34 Prinz JC, Meurer M, Reiter C, Rieber EP, Plewig G, Riethmüller G: Treatment of severe cutaneous lupus erythematosus with a chimeric CD4 monoclonal antibody, cM-T412. *J Am Acad Dermatol* 1996;34:244–252.
- 35 Booken N, Schumann T, Fuchslocher M, Goerdts S, Goebeler M: Successful therapy of discoid lupus erythematosus with efalizumab (in German). *Hautarzt* 2009, E-pub ahead of print.
- 36 Rodríguez-Lojo R, Paradelo S, Martínez-Gómez W, Fernández-Torres R, Fonseca E: Refractory discoid lupus erythematosus: response to efalizumab. *J Eur Acad Dermatol Venereol* 2009;23:1203–1205.
- 37 Lowes MA, Chamian F, Abello MV, Fuentes-Duculan J, Lin SL, Nussbaum R, Novitskaya I, Carbonaro H, Cardinale I, Kikuchi T, Gilletteau P, Sullivan-Whalen M, Wittkowski KM, Papp K, Garovoy M, Dummer W, Steinman RM, Krueger JG: Increase in TNF- α and inducible nitric oxide synthase-expressing dendritic cells in psoriasis and reduction with efalizumab (anti-CD11a). *Proc Natl Acad Sci USA* 2005;102:19057–19062.
- 38 Berthelot C, Nash J, Duvic M: Coexistent psoriasis and lupus erythematosus treated with alefacept. *Am J Clin Dermatol* 2007;8:47–50.
- 39 Krueger GG, Papp KA, Stough DB, Loven KH, Gulliver WP, Ellis CN: A randomized, double-blind, placebo-controlled phase III study evaluating efficacy and tolerability of 2 courses of alefacept in patients with chronic plaque psoriasis. *J Am Acad Dermatol* 2002;47:821–833.
- 40 Yednock TA, Cannon C, Fritz LC, Sanchez-Madrid F, Steinman L, Karin N: Prevention of experimental autoimmune encephalomyelitis by antibodies against $\alpha\beta_1$ integrin. *Nature* 1992;356:63–66.
- 41 Tieng AT, Peeva E: B-cell-directed therapies in systemic lupus erythematosus. *Semin Arthritis Rheum* 2008;38:218–227.